Remarks/Arguments

Claims 1-52 are pending in this Application. Claims 9-46 and 48-52 have been withdrawn as being drawn to an unelected invention. In the Office Action mailed December 12, 2005, the Examiner:

1. objected to the Specification for failing to provide proper antecedent basis for the claimed subject matter;
2. objected to Claim 4 for informalities;
3. rejected claims 4, 5, 6 and 7 under 35 U.S.C.§ 112, second paragraph as being indefinite;
4. rejected claims 1-3, 508 and 47 under 35 U.S.C.§ 102(b) as being anticipated by Awasthi et al. (Biochemistry 2001;40:4159-4168);

Specification

On page 3 of the Office Action, the Examiner objected to the Specification, stating "While it is now that RalBP1 and RLIP76 are synonyms for each other (see iHOP database attached), the Examiner suggests that the Specification be amended to correctly identify what applicants are now claiming." To this end, Applicants point out that paragraph [0064] of the specification includes the following statement to identify what Applicants are claiming:

> [0064] As described, RLIP76 (also referred to as RALBP1 or Ral-binding protein) is a glutathione-conjugate transporter that is a critical component of stress-response in cultured cells and provides protection from stressors including heat, oxidant chemicals, chemotherapeutic agents, UV irradiation and X-irradiation.

Nonetheless, as requested by the Examiner, Applicants respectfully submit amendments to the specification that begin on page 2 of this paper, in which paragraphs [0010]-[0015], [0024], and [0088]-0097] that further describe various aspects of the invention are amended to replace RLIP76 with RalBPI. No new matter is included with these amendments. Applicants respectfully request entry and acceptance of the amended paragraphs.

Claim Objection

On page 4 of the Office Action, the Examiner objected to Claim 4 for being drawn to portions of a non-elected invention. Applicants respectfully submit amended Claim 4, amended to remove portions of the claim drawn to a non-elected invention, namely "bioreactor, soil, water, spill, process waste stream, manufacturing waste chemical waste, laboratory waste, hospital waste, and combinations thereof." Entry and allowance of amended Claim 4 is respectfully requested.

Claims Rejection – 35 U.S.C. § 112, second paragraph

On page 4 of the Office Action, the Examiner rejected Claims 4, 5, 6 and 7 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In Claim 4 the term "reside is said to be a relative term that renders the claim indefinite. Applicants respectfully submit amended Claim 4, amended to replace the term "reside" with "are present" as particularly pointed out in the specification at, for example, paragraph [0011], a portion of which is provided below.

> [0011] . . . Toxic compounds may be present in an organism, mammalian cell, transfected mammalian cell, bioreactor, soil, water, spill, process waste stream, manufacturing waste chemical waste, laboratory waste, hospital waste, and combinations thereof, to which the proteoliposome is then added.

In Claims 5, 6 and 7, the limitation "wherein adding" is said to have insufficient antecedent basis. Applicants respectfully submit amended Claim 5, amended to remove the indefinite term "when adding." Claims 5, 6, and 7 are further amended to further define each claim. For example, Claim 5 is amended to recite "wherein the proteoliposome reduces the <u>final</u> concentration of <u>the one or more</u> toxic compounds" (emphases added to show amended text). Claim 6 is amended to recite, "wherein the proteoliposome protects against further contamination with <u>the</u> one or more toxic compounds" (emphases added to show amended text). Claim 7 is amended to recite, "wherein the proteoliposome prevents accumulation of <u>the one or more</u> toxic compounds." Amended claims do not add new matter and are believed to particularly point and distinctly claim subject matter

regarded as the invention. Entry and allowance of amended Claims 5, 6 and 7 are respectfully requested.

Claims Rejection – 35 U.S.C. § 112, first paragraph

On page 5 of the Office Action, the Examiner rejected Claims 1-8 and 47 for containing subject matter not describe in the specification in a way as to reasonably convey to one skilled in the relevant art that the Applicants, at the time the application was filed, has possession of the claimed invention. The Examiner states "a careful review of the specification as originally filed does not appear to have support for the limitation 'that delivers the effective amount of RalBP1 for transport of toxic compounds without the assistance of a co-transport molecule." Applicants point to paragraph [0057] of the originally filed application that states "small cell lung cancer cells (H82) were loaded with RLIP76 by incubating with RLIP76 encapsulated in artificial liposomes." No additional co-transport molecule was added to the cells. The paragraph and those following it further disclose that cells were irradiated and their growth index compared with cells loaded with artificial liposomes (in which no additional co-transport molecule was added) and unloaded cells (in which no additional co-transport molecule was added). The measurements shows that cells loaded with RLIP76 proteoliposomes maintained growth while cells loaded with artificial liposomes and unloaded cells had no growth (see Figure 6). Figure 7 further points out the role RLIP76 (RalBP1) plays in transporting reactive oxygen species (ROS), a by-product of irradiation, from cells. One skilled in the relevant art will appreciate and know that the loaded proteoliposomes delivered an effective amount of RalBP1 to the cells for transport of the toxic compounds without the assistance of a co-transport molecule. Applicants further point to paragraph [0067] of the originally filed application in which loss of RLIP76 (RIP1-/-, knockout mice) were treated with a RLIP76 proteoliposome injection and survived irradiation as compared with the same knockout mice treated with only an artificial liposome injection and did not survive. (see Figure 9D) No additional co-transport molecule was added to either animal. One skilled in the relevant art will appreciate and know that the loaded proteoliposomes delivered an effective amount of RalBP1 to the animals for

transport of the toxic compounds without the assistance of a co-transport molecule. In fact, Applicants point to paragraph [0069] that states "A single dose of RLIP76-liposomes containing 200 μg purified RLIP76 administered i.p. followed 48 h later by sacrificing the animals and analyzing tissues immunologically for presence of RLIP76 showed convincingly that these liposomes could be used to deliver RLIP76 to all tissues of RIP1-/- mice." (see Figure 9B). Accordingly, Applicants have pointed to clear support and specific examples of Claims 1-8 and 47 in the specification as filed. In addition, Applicants refer to paragraph [0071] in which it is stated that delivery of RLIP76 to tissue reverse the sensitivity to the toxic compound. To this end, Applicants provide amended Claim 1 and 47, amended to include "a proteoliposome that delivers to a tissue the effective portion of RalBP1." [Emphasis added to indicate amended text.] Applicants submit that the specification reasonably conveys to one skilled in the relevant art that the Applicants, at the time the application was filed, has possession of the claimed invention. Entry and allowance of amended Claims 1 and 47, and claims depending therefrom, as provided in the Listing of Claims beginning on page 2 of this paper, are respectfully requested.

On page 6 of the Office Action, the Examiner rejected Claims 1-8 and 47 for containing subject matter not described in the specification in a way as to reasonably convey to one skilled in the relevant art that the Applicants, at the time the application was filed, has possession of the claimed invention. The Examiner states:

> ". . . the claims are inclusive of a genus of proteoliposomes consisting of a liposome and an effective portion of RalBP1. However, the written description in this case only sets for the a proteoliposome consisting of a liposome and recombinant RalBP1 consisting of the amino acid sequence of SEQ ID NO:2 or two primary fragments of RalBP1, C-RLIP76$^{410-654}$ and N-RLIP$^{1-367}$. . . However, the written description only reasonably conveys a proteoliposome consisting of a liposome and recombinant RalBP1 consisting of the amino acid sequence of SEQ ID NO:2 or two primary fragments of RalBP1, e.g., C-RLIP76$^{410-654}$ and N-RLIP$^{1-367}$ in association with transport of toxic compounds."

Applicants respectfully disagree with this statement and point out that in the specification, it is clearly disclosed that transport requires two ATP-dependent binding regions of RLIP76 (see

paragraph [0048]) and that transport of toxic compounds via RLIP76 requires such ATP-dependent transport, as evidenced in cells (see, e.g., paragraphs [0052], [0054], [0059]), in animals (see, e.g., paragraphs [0067], [0071], [0074]) and inside-out vesicles (see, e.g., paragraph [0072]). Applicant further points out that in none of these examples is transport stated to be limited, as the Examiner suggests, to "a proteoliposome consisting of a liposome and recombinant RalBP1 consisting of the amino acid sequence of SEQ ID NO:2 or two primary fragments of RalBP1, e.g., C-RLIP76$^{410\text{-}654}$ and N-RLIP$^{1\text{-}367}$." To this end, Applicants have amended Claims 1 and 47 to include "wherein the effective portion of RalBP1 includes two ATP binding regions for ATP-dependent transport of the one or more toxic compounds." No new matter is introduced with this amendment. Entry and allowance of amended Claims 1 and 47 as provided in the Listing of Claims beginning on page 8 of this paper are respectfully requested

Applicant further points out that, by recitation of a number of species as provided below, one of ordinary skill in the art will recognize that human RLIP76, as disclosed in the instant Application, is both structurally and functionally similar to homologs found in mice and rats. For example, the specification discloses that the coding sequence of RLIP76 in *homo sapiens* (see Fig. 2 of the instant Application and NCBI, NP 006779) is substantially similar to the protein in rats (see paragraphs [0037] and [0038] of the instant Application). The fragments referred to by the Examiner as C-RLIP76$^{410\text{-}654}$ and N-RLIP$^{1\text{-}367}$ are identified as degraded products of RLIP76 (see paragraphs [0040], and Figure 9A and 9B). Moreover, as evidenced in a reference by Qauroni and Paul, provided as Exhibit A, two tables, B and C, on page 710, there is high DNA sequence and amino acid sequence similarity, respectively, between human RLIP76 and its homologs in rat (noted as RalBP1) and mouse (noted as RIP1). Exhibit B, a reference to Cantor, et al., provide further evidence of functional similarities between the rat homolog (noted as RalBP1), as compared with the human protein (described in the instant invention and in Julien-Flores, et al., provided as Exhibit C). Such similarities include binding to GTP-bound form of RalA and Rho-GTPase activating protein domain (see Abstract of Cantor et al. and Julien-Flores et al. and paragraph [0047] of instant Application) Similarly, Exhibit D, a reference to Park and Weinberg, provide evidence of

functional similarities between the mouse homolog (noted as RIP1), as compared with the human protein described in the instant invention, including binding to GTP-bound form of RalA (see Abstract and page 2352, Col. 2 of Park and Weinberg and Abstract of Julien-Flores et al.) and activating Rho/Rac family of GTPases (see Abstract of Park and Weinberg and Abstract of Julien-Flores et al.). Accordingly, Applicants submit that the specification as well as that was known to one of ordinary skill in the art at the time the invention was filed make clear that the Applicant is allowed the full breadth of the claim, which includes an effective portion of RalBP1 that includes two ATP binding regions for ATP-dependent transport of the one or more toxic compounds.

Claims Rejection – 35 U.S.C. §102(b)

On page 5 of the Office Action, the Examiner rejected Claims 1-8 and 47 for being anticipated by Awasthi et al. However, Applicants submit that Awasthi, et al., does not teach or suggest each and every element of amended Claim 1 nor the claimed invention as a whole. For example, Awasthi, et al., do not teach or suggest contacting a liposome with an effective portion of RalBP1 in the presence of one or more toxic compounds to create a proteoliposome that delivers to the effective portion of RalBP1 for transport of the one or more toxic compounds without the assistance of a co-transport molecule. Instead, Awasthi et al., merely reconstituted crude lystaes of membrane and soluble fractions of E. coli having a truncated fragment of RLIP76, which do not, alone, catalyze ATP-dependent transport of a chemical. Using crude lysate samples having only a portion of RLIP76 that does not catalyze ATP-dependent transport of a chemical is not equivalent to creating a proteoliposome that delivers to the effective portion of RalBP1 for transport of the one or more toxic compounds and wherein the effective portion of RalBP1 includes two ATP binding regions for ATP-dependent transport of the one or more toxic compounds. For the reasons set forth herein, Applicants respectfully submit that Claims 1-8 and 47 are not anticipated by Awasthi et al.

Conclusion

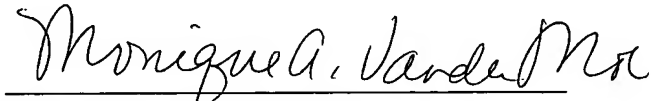
Consideration for and allowance of the claims provided in the Listing of Claims beginning on page 8 of this paper are respectfully requested for the reasons set forth herein. Accordingly, favorable consideration for and allowance of these claims are respectfully requested. No new matter has been introduced with this Amendment.

A Petition for Extension of Time for one month with the required fees accompany this response. No additional fees are believed due. If this is incorrect, Applicants hereby authorize the Commissioner to charge such additional fees, other than the issue fee, that may be required by this paper to Deposit Account No. 07-0153.

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: April 12, 2006.

Respectfully submitted,
GARDERE WYNNE SEWELL LLP



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